UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/509,533 | 05/26/2005 | David J. Waxman | 701586-52522 | 1019 |

50607 7590 03/24/2009

RONALD I. EISENSTEIN
100 SUMMER STREET
NIXON PEABODY LLP
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| NGUYEN, QUANG | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 03/24/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/509,533 | WAXMAN ET AL. | |
| | Examiner | Art Unit | |
| | QUANG NGUYEN, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,5-11,13-18,31-33,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5-11, 13-18, 31-33 and 37-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/20/09 has been entered.

Applicant elected previously the following species: (a) p35 as a species of apoptosis inhibiting agent; (b) cytochrome P450 as a species of a pro-drug activating enzyme; (c)) cyclophosphamide and other P450 prodrugs including bioreductive agents activated by P450 and/or NADPH-P450 reductase as a species of the prodrug; (d) p53 as a species of a factor promoting apoptosis; and (e) Trail as a species of a death receptor ligand.

Amended claims 1, 3, 5-11, 13-18, 31-33 and 37-38 are pending in the present application, and they are examined on the merits herein with the above elected species.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 and 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Melcher et al. (British Journal of Cancer 78:144-145, 1998). ***This is a new ground of rejection.***

Melcher et al already taught transfecting the CMT93tk line, the colorectal tumor CMT93 cell line already transfected with HSV thymidine kinase, with a retrovirus encoding bcl2 in an attempt to block apoptotic cell death during HSVtk/GCV killing; and they found that transfected cells are still sensitive to GCV *in vitro* but show greatly reduced amounts of apoptotic cell death as judged by DNA ladders and propidium iodie staining (see the entire abstract). The results of Melcher et al indicated at least that coexpression of bcl2 with HSV thymidine kinase in tumor cells increases non-apoptotic cell death on ganciclovir treatment, and they proposed that necrotic cell death *in vivo* may provide a potent immunostimulatory signal that serves as a "danger" signal to allow the breaking of tolerance to tumour antigens.

The teachings of Melcher et al meet all the limitation of the instant broad claims. Therefore, the reference anticipates the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5-11, 13 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382), Bullock et al. (Exp. Hematol. 21:1640-1647, 1993) and Melcher et al. (British Journal of Cancer 78:144-145, 1998). ***This is a new ground of rejection.***

With respect to the elected species, Waxman et al disclose methods of killing neoplastic cells (e.g., melanoma, pancreatic cancer, lung and gastrointestinal cancer, breast cancer, hepatoma) in both *in vitro* and in a mammalian patient, including a human patient, using at least NADPH-cytochrome P450 reductase (RED) gene transfer in combination with cytochrome P450 gene transfer to enhance the sensitivity of neoplastic cells to anti-cancer drugs that are activated by P450 enzymes, **wherein the P450 gene and the RED gene are delivered using one or more viral vectors** (e.g., retrovirus, adenovirus, and others), the cytochrome P45 gene is a mammalian gene such as P450 1A1, 1A2, 1B1, 2B1, 2B2, 2B4 and others and the P450-activated chemotherapeutic agent is cyclophosphamide (CPA), ifosfamide (IFA) or any other

P450-metabolized chemotherapeutic drug (See at least Summary of the Invention, pages 7-14; page 40, lines 27-30). Waxman et al further teach that the P450/RED gene therapy method may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases, and cytokines such as IL-2, IL-4 and IL-12; as well as with other established gene/produrg activation systems such as ganciclovir/HSV-TK (page 12, first full paragraph). Waxman et al also teach targeting specificity for P450 and RED gene delivery is facilitated by "transcriptional targeting" including the use of tumor-specific or tumor-selective DNA enhancer sequences (page 12, second full paragraph; page 31, first full paragraph). Waxman et al also disclose that although the viral genomes of the viral vectors used in the methods should be modified to remove or limit their ability to replicate, however, **replication conditional viruses** are also useful, such as a herpes virus with an inactivated viral ribonucleotide reductase gene that selectively delivered P450 2B1 to tumor cells that overexpress the mammalian ribonucleotide reductase enzyme which is required for this modified virus to replicate (page 33, line 27 continues to line 11 of page 34). Waxman et al also note that some therapeutic enhancement may also be anticipated in tumor cells with high levels of endogenous RED expression (page 55, lines 11-13); **tumor cells transfected with both P450/RED genes (e.g., 9L/2B6/reducase cells) are themselves more chemosensitive and more readily killed by CPA and IFA** (see Fig. 15, and page 70, lines 12-13); and **current gene therapy technologies are limited by their inability to deliver prodrug activation or other therapeutic genes to a population of tumor**

**cells with 100% efficiency and bystander cytotoxicity resultting when active drug metabolites diffuse or otherwise transferred from their site of generation within a transduced tumor cell to a neighboring, naïve tumor cell leads to significant tumor regression even when a minority of tumor cell is tranduced with the prodrug activation gene** (page 3, lines 15-28).

Waxman et al do not teach methods of killing neoplastic cells further comprising the step of transducing neoplastic cells containing a vector encoding a prodrug activating enzyme with a vector encoding an apoptosis inhibiting agent.

At the effective filing date of the present application, Bilbao et al already disclosed at least a method **to prolong or enhance transgene expression (up to 2 log increase)**, including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, **due to the attenuation of expression of the transferred therapeutic gene based at least in part due to the cytotoxic effects of the viral products** (see at least the abstract; page 18, line 10 continues to line 3 of page 19; page 19, line 28 continues to line 5 of page 20; examples 26). **Bilbao et al also taught specifically that at least a toxin gene has been selectively delivered for expression in cancer cells to achieve their eradication in a molecular chemotherapy approach** (page 2, lines 15-27). Bilbao et al further state that **"Strategies to prolong the expression of transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility"** (page 52, lines 6-10).

Additionally, Bullock et al already taught that 4-hydroperoxycylco-phosphamide (4-HC), **a P450-activated cyclophosphamide (CPA) induced internucleosomal DNA fragmentation characteristic of apopotosis or programmed cell death as well as significant reduction in bcl-2 in human myeloid leukemia HL60 cells** (see at least the abstract).

Furthermore, at the effective filing date of the present application Melcher et al also taught transfecting the CMT93tk line, **the colorectal tumor CMT93 cell line already transfected with HSV thymidine kinase, with a retrovirus encoding bcl2 in an attempt to block apoptotic cell death during HSVtk/GCV killing; and they found that although the transfected cells showed greatly reduced amounts of apoptotic cell death as judged by DNA ladders and propidium iodie staining, the transfected cells were still sensitive to GCV *in vitro*** (see the entire abstract).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Waxman et al. by further comprising at least the step of transducing neoplastic cells already transduced with both P450/RED genes with a vector encoding an apoptosis inhibiting agent, such as Bcl-2, in order to achieve maximal intratumoral chemotherapeutic drug activation via enhanced expression levels of both P450/RED genes and/or delayed transiently the death of tumor cells tranduced with both P450/RED genes so to prolong their production and secretion of cytotoxic drug metabolites to neighboring native tumor cells to attain a prolonged bystander cytotoxicity that is known to lead to significant tumor regression, in light of the teachings of Bilbao et al, Bullock et al and Melcher et al. Please note that Waxman et al already

disclosed that **tumor cells transfected with both P450/RED genes are themselves more readily killed by CPA and IFA.**

An ordinary skilled artisan would have been motivated to carry out the above modification **in order to achieve maximal intratumoral chemotherapeutic drug activation via enhanced expression levels of both P450/RED genes and/or delayed transiently the death of tumor cells tranduced with both P450/RED genes so to prolong their production and secretion of cytotoxic drug metabolites to neighboring native tumor cells to attain a prolonged bystander cytotoxicity that is known to lead to significant tumor regression**. Bilbao et al already demonstrated successfully a method to prolong or enhance transgene expression (up to 2 log increase), including a therapeutic transgene expression, in a cell by transfecting the cell with a recombinant adenoviral vector encoding an anti-apoptotic Bcl-2 to co-express the Bcl-2 gene with the transgene in the same cell, and state specifically state that "Strategies to prolong the expression of transgenes delivered by adenovirus vector, even in the context of diseases in which transient effects may be sought, are essential requirements for achieving clinical utility". Furthermore, Melcher et al and Bullock et al already disclosed respectively that **tumor cells even transfected with a recombinant vector encoding bcl-2 were still sensitive to GCV; and that 4-hydroperoxycyclophosphamide (4-HC) which is a P450-activated CPA induced internucleosomal DNA fragmentation characteristic of apoptosis and significant reduction of bcl-2 in leukemia cells.**

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Bullock et al. and Melcher et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 14-18 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382), Bullock et al. (Exp. Hematol. 21:1640-1647, 1993) and Melcher et al. (British Journal of Cancer 78:144-145, 1998) as applied to claims 1, 3, 5-11, 13 and 37-38 above, and further in view of Robertson et al (US 6,709,866) and Griffith et al. (US 6,900,185). ***This is a new ground of rejection.***

The combined teachings of Waxman et al, Bilbao et al, Bullock et al and Melcher et al were already presented above. However, none of the references teaches specifically the use of a vector comprising a nucleic acid encoding an apoptosis inhibiting agent operably linked to a regulatable promoter and/or further comprising a nucleic acid encoding a death receptor ligand, particularly Trail (the elected species) or a factor promoting apoptosis, particularly p53 (elected species) expressed under control of a regulatable promoter, even though Waxman et al teach specifically that the P450/RED gene therapy method may also be combined with other established cancer therapeutic genes, including tumor suppressor genes, such as p53, apoptotic factors, such as bax, tumor necrosis factor alpha, and caspases, and cytokines.

However, at the effective filing date of the present application Robertson et al already taught at least the use of a recombinant viral vector expressing various anti-apoptotic polypeptides such as NAIP, HIAP, HIAP2, XIAP and other under the control of a regulatable promoter to inhibit death of a cell of the nervous system in a patient (see at least Summary of the Invention, particularly col. 3, lines 19-23; and cols. 20-22).

Additionally, Griffith et al already taught a method of inducing tumor cell apoptosis using Trail/Apo2-L gene transfer in a mammal, and optionally in combination with chemotherapeutic agents, radiotherapeutic agents or immune potentiating genes or proteins (see at least Summary of the Invention). Griffith et al further taught that Trail has an apparent unique ability to induce apoptosis in a wide range of transformed cell lines but not in normal tissues and cells (col. 1, lines 15-20). Griffith et al also disclosed that expression of Trail/Apo2-L gene is under the control of a promoter, including an inducible promoter or a tissue-specific promoter (col. 10, lines 1-16).

It would have been obvious for an ordinary skilled artisan to further modify the teachings of Waxman et al, Bilbao et al, Bullock et al. and Melcher et al.., by also using a vector comprising a nucleic acid encoding an apoptosis inhibiting agent operably linked to a regulatable promoter and/or further comprising a nucleic acid encoding a death receptor ligand, particularly Trail (the elected species) or a factor promoting apoptosis,, particularly p53 (elected species) expressed under control of a regulatable promoter in light of the teachings of Robertson et al. and Griffith et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because the expression of an antiapoptotic gene and/or an apopotic gene

under a regulatable promoter *in vivo* has been widely used and applied in various gene therapy applications as taught by Robertson et al. and Griffith et al. Additionally, the expression of a transgene under a regulatable promoter can be turned on or off as needed or required by the treated patients. Furthermore, an ordinary skilled artisan would also have been motivated to select Trail/Apo2-L gene transfer to treat a mammal having a cancer due to its apparent unique ability to induce apoptosis in a wide range of transformed cell lines but not in normal tissues and cells.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Bullock et al., Melcher et al., Robertson et al.; Griffith et al., and coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 3, and 5-6 **(with respect to the elected species p35)** are rejected under 35 U.S.C. 103(a) as being unpatentable over Waxman et al. (WO 99/05299) in view of Bilbao et al. (WO 99/55382), Bullock et al. (Exp. Hematol. 21:1640-1647, 1993) and Melcher et al. (British Journal of Cancer 78:144-145, 1998) as applied to claims 1, 3, 5-11, 13 and 37-38 above, and further in view of Beidler et al. (J. Biol. Chem. 270:16526-16528, 1995). ***This is a new ground of rejection.***

The combined teachings of Waxman et al, Bilbao et al, Bullock et al and Melcher et al were already presented above. However, none of the references teaches specifically the use of a vector comprising a nucleic acid encoding an apoptosis inhibiting agent which is p35.

However, at the effective filing date of the present application Beidler et al. already taught that the baculovirus p35 protein is able to interrupt a highly conserved and ubiquitous component of the death machinery because p35 inhibits TNF- and Fas-induced apoptosis, blocks the cleavage of PARP, a death substrate in the apoptotic pathway as well as blocking developmental, viral, and x-irradiation-induced cell death (see at least the abstract; page 16528, col. 1, last paragraph).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Waxman et al, Bilbao et al, Bullock et al. and Melcher et al., by also using a vector comprising a nucleic acid encoding an apoptosis inhibiting agent that is baculovirus p35 in light of the teachings of Beidler et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Beidler et al. already taught that the baculovirus p35 protein is able to interrupt a highly conserved and ubiquitous component of the death machinery.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Waxman et al., Bilbao et al., Bullock et al., Melcher et al., Beidler et al., and coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

*The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.*

At the effective filing date of the present application, Chiocca et al (US 6,602,499 with an effective filing date of 4/30/1998) already taught methods of using viral mutants for selectively killing neoplastic cells by a combination of viral mediated oncolysis and suicide gene therapy.

***Conclusion***

***No claim is allowed.***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.**

**Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.**

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within

5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/
Primary Examiner, Art Unit 1633